UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/842,637	04/27/2001	Anthony Robert Milnes Coates	Q-64007	9237

7590 04/23/2003

LAW OFFICES
SUGHRUE, MION, ZINN, MACPEAK & SEAS, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, DC 20037-3213

EXAMINER	
MARX, IRENE	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/23/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/842,637	Applicant(s) COATES ET AL.	
	Examiner Irene Marx	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The amendment filed 2/10/03 is acknowledged. Claims 2-7, 9 and 10 are being considered on the merits.

The application should be reviewed for errors. Error occurs, for example, in claim 9 (iii) in the recitation of "said test compound test compound".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-7 and 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 6, 7 and 9 are vague and indefinite in the ambiguous use of the term "strain". In claim 9 it appears to denote a single strain of bacteria within a species, which is the art recognized definition, while in claim 4 the term "bacteria strain" is used to denote undefined bacteria within an entire species. By definition, strains within a species are different. It is suggested that language such as "said bacterial strain is selected from a strain in the group consisting of the species ...".

Claim 9 is confusing and inconsistent in that the method as claimed is now drawn to a method of "identifying whether a test compound has any antibacterial activity", while the steps include using a composition having unidentified ingredients comprising the "test compound" and further is drawn to the optional isolation step of a test compound from the composition. It is unclear what is intended therein, since the origin and nature of the test compound is not disclosed. Also the claim is vague and indefinite in that the extent of has "any antibacterial activity against stationary phase bacteria" is unclear, since antibacterial activity is dose dependent. Most compounds have at least some antibacterial activity if used at a high enough concentration.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Applicants argue that the "agent" to be tested is actually a crude composition containing the test compound. However, this definition does not appear to be provided in the as filed specification.

Applicants argue that the claims now designate that a single strain is cultured. However, this recitation is ambiguous, since it appears to be equated to an entire species, containing diverse strains. See also the rejection under 35 U.S.C § 112, second paragraph.

In response to the arguments that the concentration of antibiotic employed will depend upon the bacterial strain employed and that this can be readily determined by one skilled in the art, it must be noted that this is a daunting task that involves testing the myriad of diverse bacterial strains with the myriad of diverse antibiotics having diverse effects at varying concentrations and testing for growth and reaching stationary stage and then "selecting a phenotypically antibiotic-resistant subpopulation" from any and all bacteria using any and all antibiotics. In addition, in the review provided, it is acknowledged that the numbers of non-multiplying bacteria that survive an antibiotic treatment depends on the dose, duration and the type of antimicrobial agent (page 904, col. 2) even within the same species. The claim designated steps do not define the extent to which these variables determine the success of the process with sufficient specificity to particularly point out and distinctly claim the subject matter which the applicant regards as his invention. Applicant's aim is to achieve the result of killing growing bacteria of said strain, and selecting a phenotypically antibiotic resistant subpopulation. However, the steps of the process are not delineated with sufficient particularity to address the variables involved.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-4, 6-7 and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sahm et al. taken with Pelczar, George *et al.*, Shomura *et al.* and Barth for the reasons as stated in the last Office action and the further reasons below.

The claims are directed to a process of identifying whether a test compound has any antibacterial activity against bacteria wherein resistant bacteria are produced by treating stationary cultures with at least one antibiotic to select for resistant bacteria.

Sahm *et al.* disclose a process of identifying whether a test compound has any antibacterial activity against bacteria wherein resistant bacteria are tested with various antibiotics (See, e.g., tables I and II).

The reference differs from the claimed invention in that the selection of resistant bacteria from stationary cultures is not disclosed. However, methods of selecting for bacteria resistant to antibiotics are old and well known in the art as adequately demonstrated by the Pelczar *et al.* (See, e.g., pages 373-374). In addition, George *et al.* disclose a process for obtaining resistant bacterial cells wherein the cells are grown to stationary phase (See, e.g., page 532, col. 1).

The references also differs from the claimed invention in that *E. coli* resistant to kanamycin and *S. aureus* resistant to ampicillin are not specifically disclosed. However, Shomura *et al.* disclose a screening test for antimicrobial agents effective against resistant bacteria wherein kanamycin resistant *E. coli* are taught (See, e.g., col. 4, lines 35-38) and Barth disclose a screening test for antimicrobial agents effective against resistant bacteria wherein ampicillin resistant *S. aureus* are disclosed. (See, e.g., col. 14, lines 5-8).

With respect to the "amplification" process of claim 10, Shomura *et al.* provide guidelines about maximizing the producing of the compound of interest, which is deemed to constitute "amplification" as claimed. (See, e.g., Examples 1 and 2).

One of ordinary skill in the art would have had a reasonable expectation of success in applying the screening tests taught by Sahm *et al.* to a variety of resistant bacteria produced according to the method disclosed by Pelczar *et al.*. Alternatively one of ordinary skill in the art would have had a reasonable expectation of success of assessing the effectiveness of antimicrobial agents using already known strains of antibiotic resistant bacteria, such as kanamycin-resistant *E. coli.* or ampicillin resistant *S. aureus*.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of Sahm *et al.* by assessing the effectiveness of antimicrobial agents on a large variety of bacteria wherein resistance is induced by the method of Pelczar *et al.* or by assessing effectiveness on already existing resistant bacteria, such as kanamycin resistant *E. coli* as taught by Shomura *et al.* and ampicillin resistant *S. aureus* as disclosed by Barth for the expected benefit of obtaining and testing effective chemotherapeutic agents and thus increasing the success and efficiency of the treatment dangerous bacterial infections caused by antibiotic resistant bacteria in susceptible individuals to avoid bacteremia or other complications.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sahm *et al.* taken with Pelczar *et al.*, Shomura *et al.* and Barth as applied to claims 2-4, 6-7 and 9-10 above, and further in view of Murray *et al.* and *The Merck Index.*

The references are discussed above.

The invention as claimed differs from the references in that rifampicin resistant *M. tuberculosis* is not disclosed. However, Murray *et al.* adequately demonstrate that rifampicin resistant strains are old and well known in the art. (See, e.g., page 428). Also *The Merck Index* discloses that rifampin and rifampicin are one and the same (See, e.g., item 8382).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of Sahm *et al.* by assessing the effectiveness of antimicrobial agents on a large variety of bacteria wherein resistance is induced by the method of Pelczar *et al.* or by assessing effectiveness on already existing resistant bacteria, such as kanamycin resistant *E. coli* as taught by Shomura *et al.* and ampicillin resistant *S. aureus* as disclosed by Barth or rifampicin resistant *Mycobacterium tuberculosis,* as taught by Murray *et al.* for the expected benefit of identifying effective chemotherapeutic agents and thus increasing the success and efficiency in the treatment of tuberculosis, a dangerous and increasingly prevalent bacterial infection caused more and more by antibiotic resistant *Mycobacterium tuberculosis* in susceptible individuals.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Applicant attempts to distinguish the invention over the references by arguing that genetically resistant bacteria are different from phenotypically resistant bacteria. The argument is that the latter bacteria do not multiply at the time of exposure and that these bacteria are targetted by different antibiotics. However, it is unclear how applicants ensure that the bacteria do not multiply, since even at stationary phase there are growing bacteria, even though their numbers are in equilibrium with those of non-growing bacteria. Stationary phase is the plateau of the growth curve after log growth in a culture, during which cell number remains constant. New cells are produced at the same rate as older cells die.

In addition, the arguments by counsel that "bacteria can possess two types of resistance, phenotypic and genetic" have not been substantiated with appropriate evidence. It is well settled that arguments by counsel do not constitute evidence. Moreover, no substantiation is found in the present record for "phenotypically" resistant bacteria being, in fact, different from "genotypically" resistant bacteria. After all, the phenotype of an organism is the manifestation of the gene expression in that organism.

In addition, the bacterial strains used to identify the test compounds are claimed in terms of the method by which they are produced. Since the Patent and Trademark Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make comparisons therewith, a lesser burden of proof is required to make out a case of prima facie obviousness for product-by-process claims because of their peculiar nature than when a product is claimed in the conventional manner. MPEP 2113.

In the instant case, the as filed specification appears to be directed to the testing of certain pathogenic bacteria that exhibit "dormancy *in vivo*", such as *Staphylococcus, Escherichia, Hemophilus* and *Mycobacterium.* (Specification, page 5, paragraph 2). It is noted that Applicant is attempting to extrapolate the properties of certain pathogenic bacteria to all of the myriad of diverse bacteria known and unknown with the argument that bacteria "can possess

two types of resistance "phenotypic" and "genetic" (Response, page 8). In this regard, it is unclear that the bacteria treated with test compounds in the references differ as alleged in being "genetically" rather than "phenotypically" resistant. The argument made fails to disclose a means to detect the difference.

The scope of the showing must be commensurate with the scope of claims to consider evidence probative of unexpected results, for example. In re Dill, 202 USPQ 805 (CCPA, 1979), In re Lindner 173 USPQ 356 (CCPA 1972), In re Hyson, 172 USPQ 399 (CCPA 1972), In re Boesch, 205 USPQ 215, (CCPA 1980), In re Grasselli, 218 USPQ 769 (Fed. Cir. 1983), In re Clemens, 206 USPQ 289 (CCPA 1980). It should be clear that the probative value of the data is not commensurate in scope with the degree of protection sought by the claim.

In addition, Applicants argument that "genetic resistance occurs when a gene mutates and so confers resistance to a particular antibacterial agent, i.e., a permanent resistance" (Response, page 8), fails to consider the transfer of antibiotic resistance plasmids between bacteria, for example, which is not "permanent". Therefore, these arguments are not persuasive of error in the rejection.

It is submitted that the method of identifying whether compounds have any bacterial activity against bacteria in the combined teachings of Sahm, Pelczar and George ender the claimed invention obvious, because there is nothing in the teachings of the references to require the cells to be in "exponential" rather than "stationary" phase. The bacteria in the references are not prepared by the same process, but are deemed to possess similar properties of being antibiotic resistant.

Therefore the rejection is deemed proper and it is adhered to.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Irene Marx whose telephone number is (703) 308-2922. The examiner can normally be reached on Monday through Friday from 6:30 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The appropriate fax phone number for the organization where this application or proceeding is assigned is before final (703) 872-9306 and after final, (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service whose telephone number is (703) 308-0198 or the receptionist whose telephone number is (703) 308-1235.

Irene Marx
Primary Examiner
Art Unit 1651